

Letter to the Editor

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Response to Method Errors or Unexplained Biological Information?

To the Editor:

We thank Drs de Simone and Devereux¹ for their comments and their continued contributions to the subject of allometric normalization of left ventricular mass (LVM). The authors confirm the important residual relationship between height and LVM/height^{2,7} in an independent cohort and present population-attributable risk (PAR) estimates of LV hypertrophy (LVH) defined by LVM/height^{2,7} and by LVM/height.^{1,7}

These data are best interpreted in light of the definition and usefulness of PAR estimates and the overcorrection induced by normalizing LVM to height,^{2,7} resulting in the residual relationship between height and LVM/height.^{2,7} PAR is the portion of the incidence of a disease in the population that is due to the exposure, representing the proportional reduction in average disease risk that would be achieved by eliminating the exposure from the population while distributions of other risk factors remain unchanged (assuming the exposure is causal).² In a multi-factorial disease setting like cardiovascular disease, the focus of interest is the risk associated with the modifiable exposure while other risk factors (particularly nonmodifiable factors such as height) are kept unchanged.^{2,3} Given the relationship between height and LVM/height,^{2,7} PAR estimates for LVH defined by LVM/height^{2,7} will not only reflect LVH-associated risk but also height-related risk, whatever its mechanism may be. This is problematic from the public health, biological, and clinical perspectives. First, correlates of LVH from an epidemiological perspective, or its etiologic determinants from a biological perspective, cannot be confidently addressed unless confounding by height is eliminated. Similarly, since PAR estimates for LVH defined by LVM/height^{2,7} cannot isolate LVH-related risk, part of the risk related to height may be incorrectly attributed to LVH (hence adversely influencing computations of the attributable risk for LVH). The association between height and cardiovascular risk may be mediated by multiple biological mechanisms.⁴ The biology of LVH is equally complex. Therefore, separating height from LVH is crucial to dissecting biological mechanisms related to each; this separation is achieved by normalization to height,^{1,7} but not height.^{2,7} Eliminating the influence of height on PAR is also mandatory from an empirical preventive perspective, because height is nonmodifiable; as such, failure to eliminate its influence defeats the very purpose of PAR as a public health measure. The problems with PAR estimates influenced by nonmodifiable factors can be illustrated by an extreme example, such as the PAR for cardiovascular disease associated with a biological age >20 years: despite its unquestionable extremely high value as estimated with a formula, it is meaningless regarding expected risk reductions by preventive strategies. Even if we ignored these fundamental issues, the data demonstrate that despite its artificial advantage from capturing height-associated risk, normalization to height^{2,7} does not outperform normalization to height^{1,7}. In Multiethnic Study of Atherosclerosis (MESA), PAR for hard cardiovascular events for LVH defined by LVM/height^{1,7} and LVM/height^{2,7} were 15% and 14.6%, respectively, whereas PAR for death were 11.4% and

7.7%, respectively, if anything, favoring the unbiased normalization approach. We also note that LVM/height,^{1,7} but not LVM/height,^{2,7} significantly predicted mortality in this cohort.⁵

Drs de Simone and Devereux suggest that the substantial method difference between their original reference populations and the populations studied by our group is the age span. When we purposefully omitted adjustment for gender in allometric modeling in our study, we obtained approximately cubic powers, yet on adjustment for gender, we demonstrated that the allometric power for body height is 1.7, statistically rejecting 2.7 with >99.9% confidence. Therefore, the main cause for different results is the correction for the confounding effect of gender. Our studied populations encompassed a wide age range of ≈5 decades which are the most relevant for LVH-associated morbidity and mortality. We studied large cohorts and participants from various ethnicities, allowing stratified analyses. For optimal allometric models, the effect of body size on the physiological measure needs to be isolated from confounders, such as gender, ethnicity, and age. Therefore, the narrower age range within each of our independently examined cohorts is an advantage, rather than a disadvantage, for estimation purposes. It should be emphasized that results were, however, highly consistent in the younger Asklepios cohort and the older MESA cohort. Additionally, we note that it is not advantageous to include children, adolescents, and adults in the same analyses, given the profound modifications of anatomic proportions, body composition, and metabolic needs induced by growth and sexual maturation in childhood and adolescence. Analyses of subjects from all ages without careful exclusion of age*height interactions as determinants of LVM may be misleading. By analyzing adults only, the risk of confounding by these interactions is minimized.

Finally, whereas public health statistics are important, we emphasize the equally important clinical implications of allometric normalization. Our study demonstrates the large, systematic misclassification of individuals at the extremes of the population distribution of body height when using LVM/height,^{2,7} due to the overestimation of nonlinearity, resulting in overcorrection for height in tall individuals and undercorrection in short individuals. The magnitude of misclassification is large; furthermore, the stakes of addressing the presence of LVH in individuals from the clinical standpoint are high, considering the potential impact of false reassurance or a false diagnosis. Therefore, based on available data and various public health, statistical, biological, and clinical considerations, we believe that normalization for height^{1,7} should be strongly preferred over normalization for height.^{2,7}

Sources of Funding

This work was supported by Fonds voor Wetenschappelijk Onderzoek Vlaanderen grant G.0.838.10. MESA is conducted/supported by NHLBI in collaboration with MESA Investigators. This manuscript was prepared using a limited-access dataset obtained from NHLBI and does not necessarily reflect the opinions or views of all MESA Investigators or NHLBI.

Disclosures

None.

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